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10/502,495	06/24/2005	Geoffrey Lee	21127.0008U1	5458

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EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,495	LEE ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/29/08, 09/24/08 and 11/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of applicants arguments/Remarks, declaration and IDS submitted on 11/25/08 is acknowledged.

Claims **1-14** are under prosecution.

The following rejection is necessitated by claim amendments made by applicants.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of

copending Application No. 10/332547. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the sets of claims are directed to an application system comprising a self-adhesive matrix system comprising a polymer matrix, aminolevulinic acid or a derivative of the same, in a crystalline form wherein the size of the crystals have mean diameter of between 20 microns to 200 microns, particularly, 30-190 microns or 90-160 microns. Both sets of claims require the matrix components and their amounts, and also recite the same use for the application system. Copending claims differ from the instant claims in that the co-pending claims recites ALA derivative such as an ester and instant claims recite ALA hydrochloride. However, the instant claims require ALA in addition to the ALA derivative (ester) and copending claims also recite a "comprising" phrase that allows for the presence of the ALA ester. It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to employ the application system of the co-pending application containing ALA, to apply to the precarcinogenic and cancerous skin lesions with an expectation to achieve a photodynamic diagnosis or therapeutic effect.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 10-14 recite various acid salt and acid ester or salt thereof, however applicants have not possession of all the derivatives in dermal application system with the specifics as claimed in claim 1.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as ALA derivatives used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus.* See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure of useful [any acid salt and any acid ester or salt thereof] generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at page 5 and no examples have been provided and these are not viewed as being

reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6 and 8-14 are rejected Under 35 U.S.C. 103(a) as being unpatentable over WO 95/05813 (WO) in view of US 5,856,566 ('566) and further in view of WO 97/10811 and US PG pub. 20040171881).

WO, teaches pharmaceutical compositions comprising aminolevulinic acid (ALA) and its salt applied to skin or other dermal membrane, such as in the form of a skin patch (abstract and page 5, lines 20-35) for treating cutaneous conditions. WO teaches the composition is anhydrous. WO recognizes that ALA is unstable in fluid vehicles and degrades rapidly, particularly at higher pH (page 2, last paragraph). Like the instant disclosure, WO also desires a stable ALA preparation for dermal administration (page 3, L 5-20) and suggests adding a stabilizing amount of a solid carrier to prevent or minimize degradation of ALA (page 4, L 13-23). With respect to administration, WO teaches adhesive matrix and reservoir devices i.e., pressure

sensitive adhesive matrix made of polymers such as acrylics, silicones etc (page 7-page 8). WO teaches incorporating 0.5% to 50% ALA in the matrix. WO also discloses that ALA, in addition to the meaning given in the art, is used through out the application to refer to pharmaceutically **acceptable salts of ALA, which are considered equivalent for purposes of this invention (see page 5, lines 20-25).**

WO fails to teach crystalline ALA having a particle size of less than 200 microns.

'566 teaches ALA crystals for photodynamic therapy of actinic keratoses, hair removal and other conditions (abstract, col. 9, L 11-15). '566 recognize that ALA has a very short half-life and is also very sensitive to ambient conditions (col. 2, L 7-25), particularly, the fact that aqueous solutions of ALA degrade rapidly (also recognized by instant disclosure as well as WO). In order to overcome the degradation problem, '566 suggests employing micronized crystals of ALA (col. 2, L 45-53 and L 62-67; col. 4, L 43-53 and examples in col. 10). '566 further discloses that "5-Aminolevulinic acid is also known as 5-aminolaevulinic acid, .delta.-aminolevulinic acid, .delta.-aminolaevulinic acid and 5-amino-4-oxopentanoic acid. 5-Aminolevulinic acid can be used as the salt, particularly a simple salt and especially the hydrochloride salt. 5-Aminolevulinic acid can also be used in the form of a precursor or product of 5-aminolevulinic acid. 5-Aminolevulinic acid can also be used in its pharmacologically equivalent form, such as an amide or ester. Examples of precursors and products of 5-aminolevulinic acid and pharmacologically equivalent forms of 5-aminolevulinic acid that can be used in the present invention are described in J. Kloek et al., Prodrugs of 5-Aminolevulinic Acid for Photodynamic Therapy, Photochemistry and Photobiology, Vol. 64 No. 6, December

1996, pages 994-1000; WO 95/07077; Q. Peng et al., Build-Up of Esterified Aminolevulinic-Acid-Derivative-Induced Porphyrin Fluorescence in Normal Mouse Skin, Journal of Photochemistry and Photobiology B: Biology, Vol. 34, No. 1, June 1996; and WO 94/06424, which are all incorporated by reference herein in their entirety. As used herein, all of these compounds, unless other wise noted, are referred to jointly and severally as "ALA." (see column 4, lines 5-30).

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to employ crystalline ALA or derivatives thereof, in the transdermal compositions of WO because both '566 and WO desire a stable ALA preparation that does not degrade and while WO incorporates stabilizing amounts of carrier materials, '566 suggest crystals of ALA having sizes in micrometers, which are in addition to being stable are also sterile. Further, '566 suggest that the crystalline ALA particles can also be administered in the form of solutions without any degradation problems. Thus, a skilled artisan would have expected highly sterile and extremely stable ALA/ALA derivatives/salts crystals that can be successfully delivered at the desired site and in the desired amounts. '566 do not teach the exact particle size claimed. However, 566 suggests employing ALA crystals in microparticle sizes. Accordingly, optimizing the size range of ALA crystals that are added to the transdermal matrix system of WO, without losing the stability or activity of ALA/ALA derivative/salts would have been within the scope of a skilled artisan.

The teachings of WO 95/05813 (WO) in view of US 5,856,566 ('566) have been discussed above. With regard to the suitability of nano crystals, '881 discloses that nano

crystalline formulations typically afford greater bioavailability of drug compounds (see paragraph [1426]) and WO '811 discloses the benefit of enhancing solubility and use of nano particles in photodynamic therapy (abstract title and page 3, first paragraph).

Motivated by the advantages of nano particles in photodynamic therapy and increase in bioavailability exhibited by nano crystalline drugs, it would have been obvious to one of ordinary skilled in the art at the time the invention was made to optimize the particle size of ALA/ALA derivatives as disclosed by WO '813 and result in the claimed invention with a reasonable expectation of success.

Response to Arguments

8. Applicant's arguments filed 11/25/08 have been fully considered but they are not persuasive.

The Applicant argues that "the rejection fail to establish obviousness of the claims as amended for at least four reasons. Specifically, (1) the cited publications fail to describe or suggest ALA or ALA derivative crystals having the claimed sizes_, (2) the cited publications fail to describe or suggest the use of ALA or ALA derivative crystals in a dermal application system as is claimed, (3) the cited publications fail to provide any reason to make or use micronized ALA or ALA derivative crystals in a dermal application system, and (4) Applicants have established that the described dermal application system exhibits the unexpected result of rapid release rates of ALA.

Even accepting *arguendo* that WO 813 and *'566* can properly be combined, WO 813 and *'566,* either alone or in combination, fail to disclose or suggest using ALA or ALA derivative crystals of the claimed sizes. Applicants have amended claim 1 to recite that the patch contains ALA derivative crystals which have a mean diameter of 20 micrometer to 200 micrometer. Applicants specifically note that crystals of a "few microns" are smaller than the smallest crystal size required by the claims and nothing in either WO 813 or '566 suggest crystals in the claimed size range. For at least this reason, the claims are non-obvious."

Applicant's arguments are considered but are not persuasive. While the cited prior arts do not cite the exact claimed crystal sizes, however, the teachings of WO 811 teaches that solubility of drugs that are not stable in aqueous formulation can be employed in the form of nanoparticles so as to improve the solubility. Additionally, '881 discloses that nano crystalline formulations typically afford greater bioavailability of drug compounds (see paragraph [1426]). These two references have been cited for providing motivation for producing micron sized crystals. The primary reference WO, teaches pharmaceutical compositions comprising aminolevulinic acid (ALA) and its salt applied to skin or other dermal membrane, such as in the form of a skin patch (abstract and page 5, lines 20-35) for treating cutaneous conditions. WO teaches the composition is anhydrous. WO recognizes that ALA is **unstable in fluid vehicles** and degrades rapidly, particularly at higher pH (page 2, last paragraph). Like the instant disclosure, WO also desires a **stable ALA preparation** for dermal administration (page 3, L 5-20) and suggests adding a stabilizing amount of a solid carrier to prevent or minimize

degradation of ALA (page 4, L 13-23). The '566 reference suggests employing micronized crystals of ALA (col. 2, L 45-53 and L 62-67; col. 4, L 43-53 and examples in col. 10). '566 further disclose that "5-Aminolevulinic acid is also known as 5-aminolaevulinic acid, .delta.-aminolevulinic acid, .delta.-aminolaevulinic acid and 5-amino-4-oxopentanoic acid, **5-Aminolevulinic acid can be used as the salt**, particularly a simple salt and especially the hydrochloride salt. As such, one would have been motivated to add crystallized ALA into the teachings of primary reference and accordingly, optimizing the size range of ALA crystals that are added to the transdermal matrix system of WO, without losing the stability or activity of ALA/ALA derivative/salts would have been within the scope of a skilled artisan.

In response to applicant's argument that none of the cited references disclose the exact claimed range of ALA crystals, it is the position of the examiner that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant further argues that nano particles are way smaller than the claimed mean diameter, the argument is not persuasive, applicant has claimed **mean** diameter of 20 micrometer to 200 micrometer, not the exact size of ALA crystals.

Applicant argues the merits of declaration in application no. 10/332457. This application does not relate to the instant application. The declarations filed in the instant application have been addressed below.

9. Claim 7 is rejected Under 35 U.S.C. 103(a) as being unpatentable over WO 95/05813 (WO) in view of US 5,856,566 ('566), WO 97/10811 and US PG pub. 2004/0171881) and further in view of US 5,456,745 ('745).

'566 discussed above fail to teach the claimed polymer and softener. WO teaches acrylic polymers such as Eudragit but does not teach the softener, '745 teach a flexible film forming gels made of polymeric materials such as Eudragit, cellulose, gums etc 9co1.2, L 19-67) containing moisturizers, softeners such as citric acid esters (col. 3, L 65-67) etc., and exhibits adhesive properties (col. 6, L 46-54, col. 9, L 37-60). '745 teach employing skin treatment agents in the gel films for providing treatment to skin conditions such as acne, psoriasis etc (col. 8). Thus, polymer matrix made of claimed acrylate polymers containing softeners such as citrate esters are known in the art. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to include softeners such as citrate esters, moisturizers etc., in the polymeric matrix materials that constitute the adhesives of WO containing the crystals of ALA ('566) with an expectation provide a flexible polymer comprising ALA crystals such that the polymer matrix is stable and also easy to handle. Further, preparing the matrix containing citrate and ALA by employing the suitable steps would have been within the scope of a skilled artisan.

Response to Arguments

10. Applicant's arguments filed 11/25/08 have been fully considered but they are not persuasive.

Applicant argues that none of the references teach suspension of ALA derivative crystals in a polymer matrix having a mean particle size between 20 and 200 p.m. The disclosure of '745 does not correct these deficiencies. Applicants therefore respectfully request the withdrawal of this rejection.

Applicant arguments are not persuasive. The rationale for combining the references has been discussed above. The rejections will be maintained.

Response to Declaration

11. The declaration under 37 CFR 1.132 filed 11/15/08 is insufficient to overcome the rejection of claims 1-14 based upon the obviousness rejections as set forth in the last Office action because:

With respect to the declaration, applicants show in figure 1 that the permeation or release of ALA by the instant patch was dramatically higher than the patch containing a solution. Further, figure 2A shows the release of 72.5% of ALA having a size of 20-200 microns within first 30 minutes, their size distribution in Figure 2B. While it is observed that Figure 1 shows higher release rates, the results do not reflect the exact size of ALA crystals claimed. This is because the size distribution of ALA crystals in the examples 2A and 2B varies from 90-160 microns whereas the claims recite mean size of 20 to

200 micrometers. Further, the results are not commensurate with the scope of the claimed crystal size, except claims 5 and 8, because all the other claims encompass sizes that are outside the scope of the sizes employed in the examples. Further more, the size distribution of ALA crystals (employed for figure 2B) show overlapping percentages of ALA crystal sizes and it is not clear which of the crystal sizes actually contribute to the unexpected results.

Furthermore the declaration deals with ALA only no unexpected results have been shown with respect to ALA acid salt and esters or salts thereof. The declaration does not commensurate with the scope of the disclosure. The exhibit shows approximate sizes between 20 to 200 microns not the mean diameter as claimed. Claims 10 -14 recite various derivatives, however no possession or unexpected results have been presented in disclosure or declaration for all the derivatives or representative examples.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore /

Primary Examiner, Art Unit 1612